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Ovarian Cancer and Reproductive System Biology: A Harvard Stem Cell Institution Consortium

PRINCIPAL INVESTIGATOR:
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CONTRACTING ORGANIZATION:
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14. ABSTRACT The dominant theme of the consortium is the discovery and functional analysis of genetic alterations and pathways that alter the normal self-renewal and differentiation of epithelial precursor populations and thereby produce cancer sustaining stem cells. Dominant aims include: 1) prioritizing candidates that emerge from The Cancer Genome Atlas (TCGA) through a series of functional studies; 2) testing for altered expression or function of gene candidates in human pathologic samples, with an emphasis on alterations in early stage lesions; 3) testing known genetic lesions and novel gene candidates for transformation of specific human target cells *in vitro* and validating the essential role of gene candidates in ovarian cancer stem cells; 4) developing genetically defined murine models of ovarian and germ cell cancers; 5) testing a novel genetic pathway involving Lin28A/B and the tumor suppressor microRNA *let-7* for roles in ovarian and germ cell tumor initiation and maintenance; and 6) performing chemical-genetic screens for compounds that block the Lin28/let7 pathway. The long-term goal of the Consortium is to discover the specific links between gene alterations, target cells of transformation, and the genetic pathways that drive ovarian tumorigenesis to advance early diagnosis and treatment options.

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Introduction:

With the specific purpose of bringing the research community together to outline administrative management, research and communication plans for the Ovarian Cancer Consortium, during the development phase the site leads of six organization in Boston came together to discuss the science and organizational issues related to the Consortium development.

Body:

Three meetings were organized among site leads of six organizations in Boston: George Daley for Children's Hospital Boston (CHB), Patricia Donahoe for Massachusetts General Hospital (MGH), Lindsay Frazier for Dana-Farber Cancer Institute (DFCI), Tan Ince for Brigham and Women's Hospital (BWH) and Stephen Cannistra for Beth Israel Deaconess Medical Center (BIDMC).

The group came together with three main objectives:

- Discuss the expertise of each site in the area of ovarian cancer
- Identify at each site the PIs that could make a contribution to a Consortium collaborative proposal
- Identify senior PIs that could serve as members on the Consortium Scientific Advisory Board
- Organize a think tank to hear the latest science worked on in the various institutions and discuss the details of a proposal

A think tank was organized on November 23, 2009. The meeting was attended by the following investigators:

Abu-Yusif	Adnan	MGH
Ambros	Victor	University of Massachusetts
Anago	Kosi	MGH
Arora	Natasha	CHB
Blackwell	Keith	JOS (Joslin Diabetes Center)
Cannistra	Steve	BIDMC
Colletti	Caroline	MGH
Daley	George	CHB
D'Andrea	Alan	DFCI
Dinulescu	Daniela	BWH
Donahoe	Pat	MGH
Draetta	Guilio	DFCI
Foster	Rosemary	MGH
Frazier	Lindsay	DFCI
Hagan	John	CHB
Hasan	Tayyaba	MGH
Hirsch	Michelle	BWH
Lee	Tony	MIT (Massachusetts Institute of Technology)
Lensch	Willy	CHB
Matulonis	Ursula	DFCI
Meirelles	Katia	MGH
Meyerson	Matthew	DFCI
Powers	John	CHB
Quackenbush	John	HSPH (Harvard School of Public Health)

Raghavan	Prashant	JOS
Rizzini	Claudia	HSCI
Rueda	Bo	MGH
Sarkar	Sharmistha	DFCI
Silver	Dan	DFCI
Teixeira	Jose	MGH
Tworoger	Shelley	MGH
Wei	Xiaolong	MGH
Young	Rick	MIT

The program of the think tank included and introduction by George Daley the Principal Investigator on the proposal followed by presentations from Michelle Hirsch, Lindsay Frazier, Ursula Matulonis and Shelly Tworoger that provided and update on the ongoing science in the area of clinical research in ovarian cancer. An update on recent work in the area of basic research of ovarian cancer was given by Tan Ince, Daniela Dinulescu, Keith Blackwell and Matthew Meyerson. Finally, the update on translational research in ovarian cancer was provided by Patricia Donahoe, Alan D'Andrea, George Daley, John Hogan, John Quackenbush. Presentations were followed by a round table discussion.

A follow-up think tank was held February 9, 2010. At this meeting the group narrowed down the research focus of the consortium to three main areas:

- Genomic changes responsible for initiation and maintenance of ovarian cancer
- Human primary cell culture and Murine Models of Ovarian and Reproductive Cancer
- The Lin28A/let-7 pathway in ovarian and reproductive system cancers

It was also agreed that Stephen Cannistra would serve as a scientific consultant in the next phase of the development work. This involved the organization of a series of meetings between George Daley, Stephen Cannistra and individual investigators as well as meetings of small focused sub-groups to discuss in greater details the science to be proposed in each one of the projects and to identify collaborative interactions among them.

Key Research Accomplishments: N/A

Reportable Outcomes: N/A

Conclusion:

Core project proposals were solicited from the large number of PIs, and through small group meetings a core faculty was selected to contribute to the three major sub-areas: Ovarian Cancer Genomics (Lynda Chin, James Amatruda); human primary cell culture and animal models (Dinulescu, Drapkin, Donohoe); and the Lin28/let-7 pathway (Daley, Gregory), all supported in computation by John Quackenbush. These investigators thus comprised the fundamental core of the Harvard Ovarian Cancer Consortium. Data generated during the first year activities served as the foundation for our full application to the DOD for the proposal (see full proposal). Our abstract appears below:

Consortium abstract:

The dominant theme of the consortium is the discovery and functional analysis of genetic alterations and pathways that alter the normal self-renewal and differentiation of epithelial precursor populations and thereby produce cancer sustaining stem cells. Dominant aims include: 1) prioritizing candidates that emerge from The Cancer Genome Atlas (TCGA) through a series of functional studies; 2) testing for

altered expression or function of gene candidates in human pathologic samples, with an emphasis on alterations in early stage lesions; 3) testing known genetic lesions and novel gene candidates for transformation of specific human target cells *in vitro* and validating the essential role of gene candidates in ovarian cancer stem cells; 4) developing genetically defined murine models of ovarian and germ cell cancers; 5) testing a novel genetic pathway involving Lin28A/B and the tumor suppressor microRNA *let-7* for roles in ovarian and germ cell tumor initiation and maintenance; and 6) performing chemical-genetic screens for compounds that block the Lin28/let7 pathway. The long-term goal of the Consortium is to discover the specific links between gene alterations, target cells of transformation, and the genetic pathways that drive ovarian tumorigenesis to advance early diagnosis and treatment options.

References: N/A

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